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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/785,881	02/16/2001	Marinus Petrus de Baar	4760US	4204

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TRASK, BRITT & ROSSA
P.O. Box 2550
Salt Lake City, UT 84110

EXAMINER
CHAKRABARTI, ARUN K

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 10/21/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action

Application No.	Applicant(s)
09/785,881	De Barr
Examiner	**Art Unit**
Arun Chakrabarti	1634

-- **The MAILING DATE of this communication appears on the cover sheet with the correspondence address** --

THE REPLY FILED Oct 3, 2002 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid the abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

THE PERIOD FOR REPLY [check only a) or b)]

a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☒ The proposed amendment(s) will not be entered because:

   (a) ☒ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see NOTE below);

   (c) ☒ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: The amendment, especially the phrase "single hybridization" raise new issues that would require further consideartion and/or search.

3. ☐ Applicant's reply has overcome the following rejection(s):

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☐ The a) ☐ affidavit, b) ☐ exhibit, or c) ☐ request for reconsideration has been considered but does NOT place the application in condition for allowance because:

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a) ☒ will not be entered or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____

   Claim(s) objected to: _____

   Claim(s) rejected: 1-9, 16-18, and 21-25

   Claim(s) withdrawn from consideration: _____

8. ☐ The proposed drawing correction filed on _____ is a) ☐ approved or b) ☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

10. ☐ Other:

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600

DETAILED ACTION

Specification

1. Claims 1, 2, and 16 have been amended.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CAR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1-8, 16-17 and 21-24 are rejected under 35 U.S.C. 103 (a) over Saiki et al. (U.S. Patent 4,683,194) (July 28, 1987) in view of Bagwell et al. (U.S. Patent 5,607,834) (March 4, 1997).

Saiki et al teach a method for reducing background signals in a hybridization reaction of nucleic acids involving at least two homologous probes (Abstract and Column 6, line 65 to column 7, line 28 and Column 3, line 58 to Column 4, line 5), the method comprising:

introducing a mismatch with an intended target sequence in the probe (Column 6, line 65 to Column 7, line 15); and

conducting a hybridization reaction using the at least two homologous probes (column 7, lines 16- 28).

Saiki et al teach a method in which the homologous probes are designed to detect point mutations in at least one target sequence (Abstract and Claim 15).

Saiki et al teach a method, wherein the mismatch in a nucleotide sequence comprises 1-3 nucleotides (Column 7, lines 19-25 and Claims 16 and 21 and Figure 4).

Saiki et al teach a method, wherein the mismatch in a nucleotide sequence is located between 2 and 20 nucleotides upstream or downstream of a point mutation (Figure 4).

Saiki et al teach a method of conducting a hybridization reaction (Abstract) comprising:

mixing a set of homologous probes for detecting at least one allelic variant of a nucleic acid, wherein at least one set of homologous probes comprise at least one sequence completely complementary to and specific for one of the allelic variants of the nucleic acid, except for a

specific mismatch located downstream from the site of variation (Column 3, line 58 to Column 4, line 5 and Figure 4);

detecting variants of the nucleic acid (Column 4, lines 18-19 and Claim 15); and

using the set of homologous probes to conduct the hybridization reaction (Abstract, Claim 15 and Column 3, line 58 to Column 4, line 20 and Column 6, line 65 to column 7, line 28).

Saiki et al teach a method, wherein the nucleic acids are derived from a group of pathogens (Column 10, line 59 to column 11, line 6).

Saiki et al teach a method, wherein one of the homologous probes is provided with a detectable moiety (Figure 4).

Saiki et al do not teach a method, wherein at least one of the homologous probes is a non-linear probe.

Bagwell et al teach a method, wherein at least one of the homologous probes is a non-linear probe (Abstract and Figures 1-6).

Saiki et al do not teach a method, wherein at least one non-linear probe has a length from about 15 to about 50 nucleotides.

Bagwell et al teach a method, wherein at least one non-linear probe has a length from about 15 to about 50 nucleotides (Figure 2).

Saiki et al do not teach a method, wherein at least one non-linear probe is provided with a detectable moiety.

Bagwell et al teach a method, wherein at least one non-linear probe is provided with a detectable moiety (Abstract, Figure 7 and Claim 1).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine the non-linear probe of Bagwell et al. in the method of detection of polymorphic sites in a nucleic acid sequence of Saiki et al since Bagwell et al. state, "The present invention relates to probes for use in the detection and the quantitative analysis of target molecules (Column 1, lines 9-10)". An ordinary practitioner would have been motivated to substitute and combine the non-linear probe of Bagwell et al. in the method of detection of polymorphic sites in a nucleic acid sequence of Saiki et al in order to achieve the express advantages , as noted by Bagwell et al. , of a method which provides probes for use in the detection and the quantitative analysis of target molecules.

4. Claims 1-9, 16-17, and 21-25 are rejected under 35 U.S.C. 103 (a) over Saiki et al. (U.S. Patent 4,683,194) (July 28, 1987) in view of Guo et al. (Nature Biotechnology, (1997), Vol. 15, pages 331-335).

Saiki et al teach a method for reducing background signals in a hybridization reaction of nucleic acids involving at least two homologous probes (Abstract and Column 6, line 65 to column 7, line 28 and Column 3, line 58 to Column 4, line 5), the method comprising:

introducing a mismatch with an intended target sequence in the probe (Column 6, line 65 to Column 7, line 15); and

conducting a hybridization reaction using the at least two homologous probes (column 7, lines 16- 28).

Saiki et al teach a method in which the homologous probes are designed to detect point mutations in at least one target sequence (Abstract and Claim 15).

Saiki et al teach a method, wherein the mismatch in a nucleotide sequence comprises 1-3 nucleotides (Column 7, lines 19-25 and Claims 16 and 21 and Figure 4).

Saiki et al teach a method, wherein the mismatch in a nucleotide sequence is located between 2 and 20 nucleotides upstream or downstream of a point mutation (Figure 4).

Saiki et al teach a method of conducting a hybridization reaction (Abstract) comprising:

mixing a set of homologous probes for detecting at least one allelic variant of a nucleic acid, wherein at least one set of homologous probes comprise at least one sequence completely complementary to and specific for one of the allelic variants of the nucleic acid, except for a specific mismatch located downstream from the site of variation (Column 3, line 58 to Column 4, line 5 and Figure 4);

detecting variants of the nucleic acid (Column 4, lines 18-19 and Claim 15); and

using the set of homologous probes to conduct the hybridization reaction (Abstract, Claim 15 and Column 3, line 58 to Column 4, line 20 and Column 6, line 65 to column 7, line 28).

Saiki et al teach a method, wherein the nucleic acids are derived from a group of pathogens (Column 10, line 59 to column 11, line 6).

Saiki et al teach a method, wherein one of the homologous probes is provided with a detectable moiety (Figure 4).

Saiki et al do not teach a method, further comprising amplifying a nucleic acid sequence .

Guo et al teach a method, further comprising amplifying a nucleic acid sequence (Page 331, Column 1, third paragraph and Figure 7 and Page 334, Column 1, Allele-specific PCR amplification Section).

Saiki et al do not teach a method, wherein the mismatch in a nucleotide sequence comprises 1-3 nucleotides.

Guo et al teach a method, wherein the mismatch in a nucleotide sequence comprises 1-3 nucleotides (Figure 2, legend).

Saiki et al do not teach a method, wherein at least one of the homologous probes is a non-linear probe.

Guo et al teach a method, wherein at least one of the homologous probes is a non-linear probe (Abstract and Figure 1).

Saiki et al do not teach a method, wherein at least one non-linear probe has a length from about 15 to about 50 nucleotides.

Guo et al teach a method, wherein at least one non-linear probe has a length from about 15 to about 50 nucleotides (Figures 2-5 and Table 1).

Saiki et al do not teach a method, wherein at least one non-linear probe is provided with a detectable moiety.

Guo et al teach a method, wherein at least one non-linear probe is provided with a detectable moiety (Page 335, Experimental Protocol Section, DNA sample preparation for solid-phase hybridization Subsection).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine the non-linear probe of Guo et al. in the method of detection of polymorphic sites in a nucleic acid sequence of Saiki et al since Guo et al. state, "We describe an approach to increase the discrimination of single nucleotide polymorphisms (SNPs) in DNA hybridization by means of artificial mismatches. Artificial mismatches are inserted into oligonucleotide probes using the base analog 3-nitropyrrole. A significant enhancement of the discrimination is generally obtained, with a strong dependence of the enhancement on the spacing between mismatches. The improved specificity available with this strategy is demonstrated by both solid-phase hybridization analysis and allele-specific amplification within the HLA-DRB locus (Page 331, Column 1, first line of fourth paragraph to Column 2, line 2)". An ordinary practitioner would have been motivated to substitute and combine the non-linear probe of Guo et al. in the method of detection of polymorphic sites in a nucleic acid sequence of Saiki et al. in order to achieve the express advantages , as noted by Guo et al. , of a method which provides strategy to increase the discrimination of single nucleotide polymorphisms (SNPs) in DNA hybridization by means of artificial mismatches.

5. Claims 1-9, 16-18, and 21-25 are rejected under 35 U.S.C. 103 (a) over Saiki et al. (U.S. Patent 4,683,194) (July 28, 1987) in view of Guo et al. (Nature Biotechnology, (1997), Vol. 15, pages 331-335). further in view of Cronin et al. (U.S. Patent 6,027,880) (February 22, 2000) .

Saiki et al. in view of Guo et al teach the method of claims 1-9, 16-17, and 21-25 as described above.

Saiki et al. in view of Guo et al do not teach the method, wherein the nucleic acids represent a number of HIV-variants.

Cronin et al. teach the method, wherein the nucleic acids represent a number of HIV-variants (Column 18, lines 20-26).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine the nucleic acids representing a number of HIV-variants of Cronin et al. in the method of detection of polymorphic sites in a nucleic acid sequence of Saiki et al in view of Guo et al., since Cronin et al. state, "Such capacity is valuable, e.g., for diagnosis of patients who are heterozygous with respect to a gene or who are infected with a virus, such as HIV, which is usually present in several polymorphic forms (Column 18, lines 23-26) ". An ordinary practitioner would have been motivated to substitute and combine the nucleic acids representing a number of HIV-variants of Cronin et al. in the method of detection of polymorphic sites in a nucleic acid sequence of Saiki et al in view of Guo et al. , as noted by Cronin et al. , of a method which provides capacity valuable for diagnosis of

patients who are heterozygous with respect to a gene or who are infected with a virus, such as HIV, which is usually present in several polymorphic forms.

Response to Amendment

6. In response to amendment, 112 (second paragraph) rejections are hereby withdrawn. However, 103(a) rejections are maintained properly.

Response to Arguments

7. Applicant's arguments filed on February 21, 2002 have been fully considered but they are not persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant argues that a complementary probe is not a homologous probe as used in the invention and explained what is a "homologous" probe. This argument is not persuasive because it is not clear from the explanation what is the basic difference between a complementary probe with a mismatch and a "homologous" probe. It has been explained clearly in the first office action that Guo reference teaches a complementary probe with a mismatch.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., a complementary probe is not a homologous probe) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Conclusion

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CAR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CAR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arun Chakrabarti, Ph.D. whose telephone number is (703) 306-5818.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Chantae Dessau whose telephone number is (703) 605-1237.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission via the P.T.O. Fax Center located in Crystal Mall 1. The CM1 Fax Center numbers for Technology Center 1600 are either (703) 305-3014 or (703) 308-4242. Please note that the faxing of such papers must conform with the Notice to Comply published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Arun Chakrabarti
Patent Examiner
Art Unit 1634

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600

July 1, 2002